BF

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 March 2001 (01.03.2001)

PCT

(10) International Publication Number
WO 01/14371 A1

(51) International Patent Classification[7]: C07D 405/14, 403/04, A61K 31/506, A61P 21/00

(21) International Application Number: PCT/US00/23173

(22) International Filing Date: 24 August 2000 (24.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/383,813 26 August 1999 (26.08.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/383,813 (CON)
Filed on 26 August 1999 (26.08.1999)

(71) Applicants *(for all designated States except US)*: **BERLEX LABORATORIES, INC.** [US/US]; 15049 San Pablo Avenue, P.O. Box 4099, Richmond, CA 94804-0099 (US). **PHARMACOPEIA, INC.** [US/US]; 3000 Eastpark Boulevard, Cranbury, NJ 08512 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARNAIZ, Damian, O.** [US/US]; 103 Bedford, Hercules, CA 94547 (US). **BALDWIN, John, J.** [US/US]; 621 Gypsy Hill Circle, Gwynedd Valley, PA 19437 (US). **DAVEY, David, D.** [US/US]; 3813 Painted Pony Road, El Sobrante, CA 94803 (US). **DEVLIN, James, J.** [US/US]; 1146 Upper Happy Valley Road, Lafayette, CA 94549 (US). **DOLLE, Roland, Ellwood, III** [US/US]; 550 Prince Frederick Street, King of Prussia, PA 19460 (US). **ERICKSON, Shawn, David** [US/US]; 122 Oaktree Place, Leonia, NJ 07605 (US). **McMILLAN, Kirk** [US/US]; 14 Arundel, Burlingame, CA 94010 (US). **MORRISSEY, Michael, M.** [US/US]; 129 Alta Vista Way, Danville, CA 94506 (US). **OHLMEYER, Michael, H., J.** [GB/US]; 6 Beechtree Lane, Plainsboro, NJ 08536 (US). **PAN, Gonghua** [CN/US]; 600 Meridian Street Ext. #1307, Groton, CT 06340 (US). **PARADKAR, Vidyadhar, Madhav** [IN/US]; 3 Pine Ridge Drive, Somerville, NJ 08876 (US). **PARKINSON, John** [GB/US]; 6727 Waverly Road, Martinez, CA 94553 (US). **PHILLIPS, Gary, B.** [US/US]; 3043 Shetland Drive, Pleasant Hill, CA 94523 (US). **YE, Bin** [CN/US]; Apartment 3022, 3400 Richmond Parkway, Richmond, CA 94806 (US). **ZHAO, Zuchun** [CN/US]; 5368 Cerro Sur, El Sobrante, CA 94803 (US).

(74) Agents: **ZELANO, Anthony, J.** et al.; Millen, White, Zelano & Branigan, P.C., Arlington Courthouse Plaza 1, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).

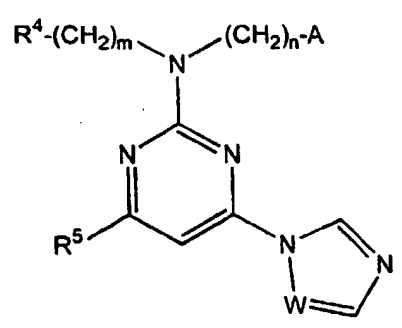
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

[Continued on next page]

(54) Title: *N*-HETEROCYCLIC DERIVATIVES AS NOS INHIBITORS



(Ya)

(57) Abstract: *N*-Heterocyclic derivatives of formula (Ya) are described herein, as well as other *N*-heterocycles, as inhibitors of nitric oxide synthase. Pharmaceutical compositions containing these compounds, methods of using these compounds as inhibitors of nitric oxide synthase and processes for synthesizing these compounds are also described herein.

WO 01/14371 A1

— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

N-HETEROCYCLIC DERIVATIVES AS NOS INHIBITORS

Field of the Invention

The invention relates to a series of *N*-heterocyclic compounds and derivatives useful as inhibitors of nitric oxide synthase (NOS) and to methods of therapy for various diseases employing those compounds.

Background of the Invention

Nitrogen monoxide (NO) has been implicated in a number of diverse physiological processes, including smooth muscle relaxation, platelet inhibition, nerve transmission, immune regulation and penile erection. Nitric oxide is produced under various conditions by virtually all nucleated mammalian cells. A number of pathologies are ascribed to abnormalities in NO production including stroke, insulin dependent diabetes, septic shock-induced hypotension, rheumatoid arthritis and multiple sclerosis. Nitric oxide is synthesized in biological tissues by an enzyme called nitric oxide synthase (NOS) which uses NADPH and molecular oxygen to oxidize L-arginine to citrulline and nitric oxide.

Nitric oxide synthase (NOS) exists in at least three isoforms, which fall into two primary categories: constitutive and inducible. Two constitutive isoforms, which are calcium and calmodulin dependent, have been identified, and one inducible isoform has been identified. The constitutive isoforms are (1) a neuronal isoform, NOS-1 or nNOS, which is found in the brain and skeletal muscles and (2) an endothelial isoform, NOS-3 or eNOS, which is expressed in the endothelium of blood vessels, the epithelium of the bronchial tree and in the brain. These constitutive isoforms are not the target of the NOS inhibitors of the present invention.

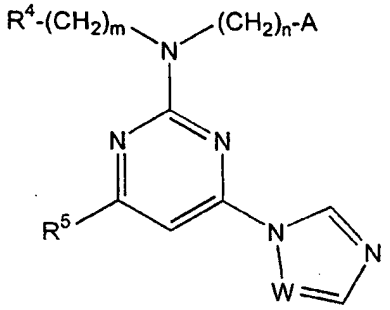
The inducible isoform (NOS2 or iNOS) is expressed in virtually all nucleated mammalian cells following exposure to inflammatory cytokines or lipopolysaccharide. Its presence in macrophages and lung epithelial cells is particularly noteworthy. The inducible isoform is neither stimulated by calcium nor blocked by calmodulin antagonists. It contains several tightly bound co-factors, including FMN, FAD and tetrahydrobiopterin.

Nitric oxide generated by the inducible form of NOS has been implicated in the pathogenesis of inflammatory diseases. In experimental animals, hypotension induced by lipopolysaccharide or tumor necrosis factor α can be reversed by NOS inhibitors. Conditions which lead to cytokine-induced hypotension include septic shock, hemodialysis and interleukin therapy in cancer patients. It is expected that an iNOS inhibitor would be effective in treating cytokine-induced hypotension. In addition, recent studies have suggested a role for NO in the pathogenesis of inflammation, and NOS inhibitors would therefore have beneficial effects on inflammatory bowel disease, cerebral ischemia and arthritis. Inhibitors of NOS may also be useful in treating adult respiratory distress syndrome (ARDS) and myocarditis, and they may be useful as adjuvants to short term immunosuppression in transplant therapy.

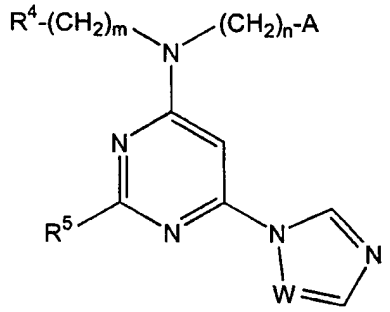
The diversity and ubiquity of NO function in physiology make the specific therapeutic targeting of NO-related phenomena an important consideration. Since endogenous NO production is the result of the actions of related but distinct isozymes, the differential inhibition of NOS isozymes allows more selective therapy with fewer side effects.

SUMMARY OF THE INVENTION

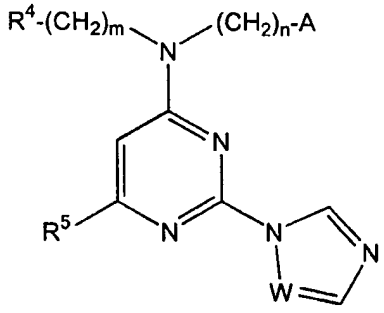
In one aspect, the invention is directed to compounds of formula (Ya), formula (Yb) and formula (Yc):



(Ya);



(Yb);



(Yc);

wherein:

n and m are each independently an integer from 1 to 4;

A is -C(O)OR^1 or -C(O)N(R^1)R^2;

each W is N or CH;

each R^1 is independently hydrogen, alkyl, aryl or aralkyl;

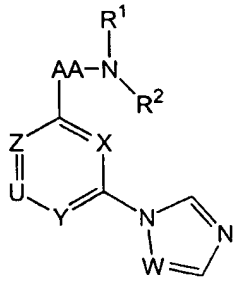
each R^2 is independently hydrogen, C_0-C_{20} alkyl, -$(CH_2)_n$-N(R^1)$_2$, heterocyclylalkyl (optionally substituted by alkyl, halo, haloalkyl or alkoxy), aralkyl (optionally substituted by halo, alkyl, alkoxy, or -N(R^1)$_2$);

R^4 is hydroxy, cyano, heterocyclyl, -N(R^1)R^2, -N(R^1)-C(O)-R^1, -N(R^1)-C(O)OR^1, -N(R^1)-S(O)$_t$-R^1, or-N(R^1)-C(O)-N(R^1)$_2$;

R^5 is hydrogen, halo, alkyl, aryl, aralkyl, or haloalkyl;

as a single stereoisomer or mixture thereto, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention is directed to compounds of formula (IV):



(IV) ;

wherein:

AA is an amino acid;

X, Y and Z are independently N or C(R^{19});

U is N or C(R^5), provided that U is N only when X is N and Z and Y are CR^{19};

W is N or CH;

R^1 and R^2 are independently chosen from the group consisting of hydrogen, optionally substituted C_1-C_{20} alkyl, optionally substituted cycloalkyl, -[C_0-C_8 alkyl]-R^9, -[C_2-C_8 alkenyl]-R^9, -[C_2-C_8 alkynyl]-R^9, -[C_2-C_8 alkyl]-R^{10} (optionally substituted by hydroxy), -[C_1-C_8]-R^{11} (optionally substituted by hydroxy), and optionally substituted heterocyclyl;

or R^1 and R^2 together with the nitrogen atom to which they are attached is an optionally substituted *N*-heterocyclyl;

R^5 is chosen from the group consisting of hydrogen, halo, alkyl, haloalkyl, optionally substituted aralkyl, optionally substituted aryl, -OR^{16}, -S(O)$_t$-R^{16}, -N(R^{16})R^{21}, -N(R^{16})C(O)N(R^1)R^{16}, -N(R^{16})C(O)OR^{16}, -N(R^{16})C(O)R^{16}, -[C_0-C_8 alkyl]-C(O)OR^{16}, -[C_0-C_8 alkyl]-C(H)[C(O)OR^{16}]$_2$, and -[C_0-C_8 alkyl]-C(O)N(R^1)R^{16};

each R^9 is independently chosen from the group consisting of haloalkyl, cycloalkyl (optionally substituted with halo, cyano, alkyl or alkoxy), carbocyclyl (optionally substituted with one or more substituents selected from the group consisting of halo, alkyl and alkoxy), and heterocyclyl (optionally substituted with alkyl, aralkyl or alkoxy);

each R^{10} is independently chosen from the group consisting of halo, alkoxy, optionally substituted

aryloxy, optionally substituted aralkoxy, optionally substituted -$S(O)_t$-R^{22}, acylamino, amino, monoalkylamino, dialkylamino, (triphenylmethyl)amino, hydroxy, mercapto, and alkylsulfonamido;

each R^{11} is independently chosen from the group consisting of cyano, di(alkoxy)alkyl, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl and dialkylaminocarbonyl;

each R^{16} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl or cycloalkyl;

R^{19} is hydrogen, alkyl (optionally substituted with hydroxy), cyclopropyl, halo or haloalkyl;

each R^{21} is hydrogen, alkyl, cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, -$C(O)R^{22}$ or -SO_2R^{22};

or R^{21} taken together with R^1 and the nitrogen to which they are attached is an optionally substituted *N*-heterocyclyl;

or R^{21} taken together with R^{16} and the nitrogen to which they are attached is an optionally substituted *N*-heterocyclyl;

each R^{22} is independently alkyl, cycloalkyl, optionally substituted aryl or optionally substituted aralkyl; and

t is zero, one or two;

as a single isomer or mixture thereof, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention is directed to pharmaceutical compositions comprising a compound of formula (Ya), formula (Yb), and formula (Yc), as described above, and a pharmaceutically acceptable carrier.

In another aspect, the invention is directed to methods of treating a condition resulting from an abnormality in nitric oxide production which comprises administering to a mammal having a condition resulting from an abnormality in nitric oxide production a therapeutically effective amount of compound of formula (Ya), formula (Yb), and formula (Yc), as described above.

Detailed Description of the Invention

Definitions

As used in this specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like. Alkyl radicals having more than eight carbon atoms are indicated herein by the notation "[C_x-C_y alkyl]" where x and y indicate the number of carbons present. Alkyl radicals may be optionally substituted by one or more substituents independently selected from the group consisting of halo, hydroxy, alkoxy, carboxy, cyano, carbonyl, alkoxycarbonyl, cyano, amino, monoalkylamino, dialkylamino, nitro,

alkylthio, amidino, aryl, heterocyclyl, aryloxy, aralkoxy, acylamino, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl.

"Alkenyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing at least one double bond and having from one to eight carbon atoms, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

"Alkynyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing at least one triple bond and having from one to eight carbon atoms, *e.g.*, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl, and the like.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above, *e.g.*, methoxy, ethoxy, propoxy, and the like.

"Alkoxycarbonyl" refers to a radical of the formula $-C(O)OR_a$ where R_a is an alkyl radical as defined above, *e.g.*, methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, and the like.

"Alkoxycarbonylalkyl" refers to a radical of the formula $-R_a-C(O)OR_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, 2-(methoxycarbonyl)ethyl, 3-(ethoxycarbonyl)propyl, 4-(*n*-propoxycarbonyl)butyl, and the like.

"Alkylsulfonylamino" refers to a radical of the formula $-N(H)S(O)_2-R_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylsulfonylamino, ethylsulfonylamino, and the like.

"Alkylsulfonyl" refers to a radical of the formula $-S(O)_2-R_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylsulfonyl, ethylsulfonyl, and the like.

"Alkylthio" refers to a radical of the formula $-S-R_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylthio, ethylthio, *n*-propylthio, and the like.

"Amidino" refers to a radical of the formula $-C(NH)-NH_2$.

"Amino" refers to a radical of the formula $-NH_2$.

"Aminocarbonyl" refers to a radical of the formula $-C(O)NH_2$.

"Aminosulfonyl" refers to a radical of the formula $-S(O)_2NH_2$.

"Aryl" refers to a phenyl or naphthyl radical. The aryl radical may be optionally substituted by one or more substituents selected from the group consisting of hydroxy, mercapto, halo, alkyl, alkenyl, alkynyl, phenyl, phenylalkyl, phenylalkenyl, alkoxy, phenoxy, phenylalkoxy, haloalkyl, haloalkoxy, formyl, nitro, cyano, cycloalkyl, hydroxyalkyl, alkoxyalkyl, phenoxyalkyl, phenylalkoxyalkyl, amidino, ureido, alkoxycarbonyamino, amino, monoalkylamino, dialkylamino, monophenylamino, monophenylalkylamino, sulfonylamino, akylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monophenylaminoalkyl, monophenylalkylaminoalkyl, acyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, and dialkylaminocarbonylalkyl, as defined herein.

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, benzyl, and the like. The aryl radical may be optionally substituted as described above.

"Aryloxy" refers to a radical of the formula $-OR_b$ where R_b is an aryl radical as defined above, *e.g.*, phenoxy and naphthoxy, and the like. The aryl radical may be optionally substituted as described above.

"Aryloxycarbonyl" refers to a radical of the formula $-C(O)OR_b$ where R_b is an aryl radical as defined above, *e.g.*, phenoxycarbonyl.

"Aralkoxy" refers to a radical of the formula $-OR_c$ where R_c is an aralkyl radical as defined above, *e.g.*, benzyloxy, and the like. The aralkyl radical may be optionally substituted as described above.

"Aralkoxycarbonyl" refers to a radical of the formula $-C(O)OR_c$ where R_c is an aralkyl radical as defined above, *e.g.*, benzyloxycarbonyl, and the like. The aralkyl radical may be optionally substituted as described above.

"Arylaminocarbonyl" refers to a radical of the formula $-C(O)N(R_b)H$ where R_b is an aryl radical as defined above, *e.g.*, phenylaminocarbonyl, and the like. The aryl radical may be optionally substituted as described above.

"Arylaminosulfonyl" refers to a radical of the formula $-S(O)_2N(R_b)H$ where R_b is an aryl radical as defined above, *e.g.*, phenylaminosulfonyl, and the like. The aryl radical may be optionally substituted as described above.

"Arylsulfonyl" refers to a radical of the formula $-S(O)_2-R_b$ where R_b is an aryl radical as defined above, *e.g.*, phenylsulfonyl, and the like. The aryl radical may be optionally substituted as described above.

"Arylsulfonylaminocarbonyl" refers to a radical of the formula $-C(O)N(H)S(O)_2R_b$ where R_b is an aryl radical as defined above, *e.g.*, phenylsulfonylaminocarbonyl, and the like. The aryl radical may be optionally substituted as described above.

"Acyl" refers to a radical of the formula $-C(O)-R_a$ and $-C(O)R_b$ where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, acetyl, propionyl, benzoyl, and the like.

"Acylamino" refers to a radical of the formula $-N(H)-C(O)-R_a$ and $-N(H)-C(O)-R_b$ where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, acetylamino, benzoylamino and the like.

"Alkylene" refers to straight or branched chain divalent radical consisting solely of carbonyl and hydrogen, containing no unsaturation and having from one to eight carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene radical may be optionally substituted by one or more substituents selected from the group consisting of alkyl, hydroxy, $-N(R^{16})R^{21}$ or $-C(O)N(R^1)R^{16}$ where R^1, R^{16} and R^{21} are as defined above in the Summary of the Invention.

"Cycloalkyl" refers to a stable 3- to 10-membered monocyclic or bicyclic radical which is saturated, and which consist solely of carbon and hydrogen atoms, *e.g.*, cyclopropyl, cyclobutyl, cyclobutyl, cyclohexyl, decalinyl and the like. Unless otherwise stated specifically in the

specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, halo, hydroxy, amino, cyano, nitro, alkoxy, carboxy and alkoxycarbonyl.

"Carboxy" refers to the radical of the formula -C(O)OH.

"Carboxyalkyl" refers to a radical of the formula $-R_a-C(O)OH$ where R_a is an alkyl radical as defined above, *e.g.*, carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, and the like.

"Di(alkoxy)alkyl" refers to a radical of the formula $-R_a(-OR_a)_2$ where each R_a is independently an alkyl radical as defined above and where the $-OR_a$ groups may be attached to any carbon in the R_a group, *e.g.*, 3,3-dimethoxypropyl, 2,3-dimethoxypropyl, and the like.

"Dialkylamino" refers to a radical of the formula $-N(R_a)R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylamino, diethylamino, (methyl)(ethyl)amino, and the like.

"Dialkylaminocarbonyl" refers to a radical of the formula $-C(O)N(R_a)R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylaminocarbonyl, methylethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, ethylpropylaminocarbonyl, and the like.

"Dialkylaminosulfonyl" refers to a radical of the formula $-S(O)_2N(R_a)R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylaminosulfonyl, methylethylaminosulfonyl, diethylaminosulfonyl, dipropylaminsulfonyl, ethylpropylaminosulfonyl, and the like.

"Halo" refers to bromo, chloro, iodo or fluoro.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

"Haloalkoxy" refers to a radical of the formula $-OR_d$ where R_d is an haloalkyl radical as defined above, *e.g.*, trifluoromethoxy, difluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy, 1-fluoromethyl-2-fluoroethoxy, 3-bromo-2-fluoropropoxy, 1-bromomethyl-2-bromoethoxy, and the like.

"Heterocyclyl" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated or aromatic. The heterocyclyl radical may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclyl radicals include, but are not limited to, azepinyl, azetidinyl, acridinyl, benzimidazolyl,

benzodioxolyl, benzodioxanyl, benzothiazolyl, benzoxazolyl, benzopyranyl, benzofuranyl, benzothienyl, carbazolyl, cinnolinyl, decahydroisoquinolyl, dioxolanyl, furyl, isothiazolyl, quinuclidinyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, perhydroazepinyl, piperidinyl, piperazinyl, 4-piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydroisoquinolyl, thienyl, thiomorpholinyl, thiomorpholinyl sulfoxide, and thiomorpholinyl sulfone. The heterocyclyl radical may be optionally substituted by R^6 as defined above in the Summary of the Invention or may be optionally substituted by one or more substituents selected from the group consisting of hydroxy, mercapto, halo, alkyl, alkenyl, alkynyl, phenyl, phenylalkyl, phenylalkenyl, alkoxy, phenoxy, phenylalkoxy, haloalkyl, haloalkoxy, formyl, nitro, cyano, amidino, cycloalkyl, hydroxyalkyl, alkoxyalkyl, phenoxyalkyl, phenylalkoxyalkyl, amidino, ureido, alkoxycarbonyamino, amino, monoalkylamino, dialkylamino, monophenylamino, monophenylalkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monophenylaminoalkyl, monophenylalkylaminoalkyl, alkylcarbonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, and imidazolyl, as defined herein.

"Heterocyclylalkyl" refers to a radical of the formula $-R_a-R_e$ where R_a is an alkyl radical as defined above and R_e is a heterocyclyl radical as defined above, *e.g.*, 2-(1,3-benzodioxol-5-yl)ethyl, and 3-(1,4-benzodioxan-6-yl)propyl, and the like.

"Monoalkylamino" refers to a radical of the formula $-N(H)R_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylamino, ethylamino, propylamino, and the like.

"Monoalkylaminocarbonyl" refers to a radical of the formula $-C(O)N(H)R_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, and the like.

"Monoalkylaminosulfonyl" refers to a radical of the formula $-S(O)_2N(H)R_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylaminosulfonyl, ethylaminosulfonyl, propylaminosulfonyl, and the like.

"*N*-heterocyclyl" refers to a heterocyclyl radical as defined above which contains at least one nitrogen atom and which is attached to the main structure through the nitrogen atom. The *N*-heterocyclyl radical may contain up to three additional hetero atoms. Examples include piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, azetidinyl, indolyl, pyrrolyl, imidazolyl, tetrahydroisoquinolyl, perhydroazepinyl, tetrazolyl, triazolyl, oxazinyl, and the like, and may be optionally substituted as described above for heterocyclyl radicals. In addition to being

optionally substituted by the substituents listed above for a heterocyclyl radical, the *N*-heterocyclyl radical may also be optionally substituted by R^6 as defined above in the Summary of the Invention.

"Phenylalkyl" refers to an alkyl radical as defined above substituted by a phenyl radical, *e.g.*, benzyl, and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution. The term "-[C_2-C_8 alkyl]-R^{10} (optionally substituted by hydroxy)" means that the alkyl has the optional substitution. The same goes for the term "-[C_1-C_8 alkyl]-R^{11} (optionally substituted by hydroxy)". The term "optionally substituted -$S(O)_iR^{22}$" means that the R^{22} substituents all have the optional substitution.

"Phenylalkenyl" refers to an alkenyl radical as defined above substituted by a phenyl radical.

The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. When the compounds of the present invention are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Suitable pharmaceutically acceptable acid addition salts for the compounds of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, *p*-toluenesulfonic, and the like. When the compounds contain an acidic side chain, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine.

"Therapeutically effective amount" refers to that amount of a compound of the invention which, when administered to a human in need thereof, is sufficient to effect treatment, as defined below, for conditions resulting from an abnormality in nitric oxide production. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the condition and its severity, and the age of the human to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Treating" or "treatment" as used herein covers the treatment of a condition in a human, which condition results from an abnormality in nitric oxide production, and includes:

(i) preventing the condition from occurring in a human, in particular, when such human is predisposed to the condition but has not yet been diagnosed as having it;

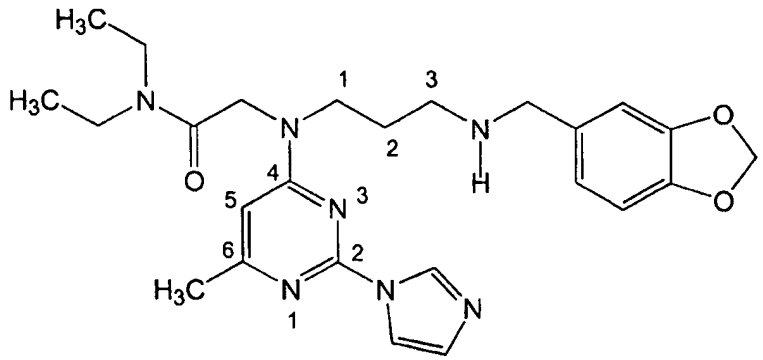
(ii) inhibiting the condition, *i.e.*, arresting its development; or

(iii) relieving the condition, *i.e.*, causing regression of the condition.

The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield.

Most of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

The nomenclature used herein is a modified form of the I.U.P.A.C. nomenclature system wherein the compounds of the invention are named herein as amide derivatives. For example, the following compound of the invention:



is named herein as 2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N,N*-diethylacetamide. Unless otherwise indicated, compound names are intended to include any single stereoisomer, enantiomer, racemate or mixtures thereof.

Utility of the Compounds of the Invention

Nitric oxide generated by the inducible form of nitric oxide synthase (i-NOS) has been implicated in the pathogenesis of numerous inflammatory and autoimmune diseases and also in diseases which are generally not regarded as inflammatory, but nevertheless may involve cytokines which locally up-regulate i-NOS. The compounds of the invention, alone or in combination with other pharmaceutical agents, are therefore useful in treating mammals,

preferably humans, having a condition resulting from an abnormality in nitric oxide production. Such conditions include, but are not limited to, the following:

Multiple sclerosis (Parkinson, J.F. *et al., J. Mol. Med.* (1997), Vol. 75, pp. 174-186); stroke or cerebral ischemia (Iadecola, C. *et al., J. Neurosci.* (1997), Vol. 17, pp. 9157-9164); Alzheimer's disease (Smith, M.A. *et al., J. Neurosci.* (1997), Vol. 17, pp. 2653-2657; Wallace, M.N. *et al., Exp. Neurol.* (1997), Vol. 144, pp. 266-272); HIV dementia (Adamson D.C. *et al., Science* (1996), Vol. 274, pp. 1917-1921); Parkinson's disease (Hunot, S. *et al., Neuroscience* (1996), Vol. 72, pp. 355-363); meningitis (Koedel, U. *et al., Ann. Neurol.* (1995), Vol. 37, pp. 313-323); dilated cardiomyopathy and congestive heart failure (Satoh M *et al., J. Am. Coll. Cardiol.* (1997), Vol. 29, pp. 716-724); atherosclerosis (Wilcox, J.N. *et al., Arterioscler. Thromb. Vasc. Biol.* (1997), Vol. 17, pp. 2479-2488); restenosis or graft stenosis, septic shock and hypotension (Petros, A. *et al., Cardiovasc. Res.* (1994), Vol. 28, pp. 34-39); hemorrhagic shock (Thiemermann, C. *et al., Proc. Natl. Acad. Sci.* (1993), Vol. 90, pp. 267-271); asthma (Barnes, P.J., *Ann. Med.* (1995), Vol. 27, pp. 389-393; Flak, T.A. *et al., Am. J. Respir. Crit. Care Med.* (1996), Vol. 154, pp. S202-S206); adult respiratory distress syndrome, smoke or particulate-mediated lung injury (Ischiropoulos, H. *et al., Am. J. Respir. Crit. Care Med.* (1994), Vol. 150, pp. 337-341; Van Dyke, K., *Agents Actions* (1994), Vol. 41, pp. 44-49); pathogen-mediated pneumonias (Adler, H. *et al., J. Exp. Med.* (1997), Vol. 185, pp. 1533-1540); trauma of various etiologies (Thomae, K.R. *et al., Surgery* (1996), Vol. 119, pp. 61-66); rheumatoid arthritis and osteoarthritis (Grabowski, P.S. *et al., Br. J. Rheumatol.* (1997), Vol. 36, pp. 651-655); glomerulonephritis (Weinberg, J.B. *et al., J. Exp. Med.* (1994), Vol. 179, pp. 651-660); systemic lupus erythematosus (Belmont, H.M. *et al., Arthritis Rheum.* (1997), Vol. 40, pp. 1810-1816); inflammatory bowel diseases such as ulcerative colitis and Crohn's disease (Godkin, A.J. *et al., Eur. J. Clin. Invest.* (1996), Vol. 26, pp. 867-872; Singer, I.I. *et al., Gastroenterology* (1996), Vol. 111, pp. 871-885); insulin dependent diabetes mellitus (McDaniel, M.L., *et al., Proc. Soc. Exp. Biol. Med.* (1996), Vol. 211, pp. 24-32); diabetic neuropathy or nephropathy (Sugimoto, K. and Yagihashi, S., *Microvasc. Res.* (1997), Vol. 53, pp. 105-112; Amore, A. *et al., Kidney Int.* (1997), Vol. 51, pp. 27-35); acute and chronic organ transplant rejection (Worrall, N.K. *et al., Transplantation* (1997), Vol. 63, pp. 1095-1101); transplant vasculopathies (Russell, M.E. *et al.,* (1995), Vol. 92, pp. 457-464); graft-versus-host disease (Kichian, K. *et al., J. Immunol.* (1996), Vol. 157, pp. 2851-2856); psoriasis and other inflammatory skin diseases (Bruch-Gerharz, D. *et al., J. Exp. Med.* (1996), Vol. 184, pp. 2007-2012); and cancer (Thomsen, L.L. *et al., Cancer Res.* (1997), Vol. 57, pp. 3300-3304).

The compounds of the current invention may also be useful for the management of male and female reproductive functions when used alone or combined with other drugs commonly used for these indications. Examples, without implied limitation, include: inhibition of fertilization, endometrial receptivity and implantation (alone or in combination with a progesterone antagonist); post-coital contraception (alone or in combination with a progesterone antagonist);

induction of abortion (in combination with an antiprogestin and in further combination with a prostaglandin); control and management of labor and delivery; treatment of cervical incompetence (alone or in combination with progesterone or a progestin); treatment of endometriosis (alone or in combination with other drugs, including LHRH-agonists/antagonists, antiprogestins orprogestins by either sequential application or by concomitant administration). See, for example, the following references: Chwalisz, K. *et al., J. Soc. Gynecol. Invest.* (1997), Vol. 4, No. 1 (Supplement), page 104a, which discusses the inhibition of fertilization, endometrial receptivity and implantation, or post-coital contraception, alone or in combination with a progesterone antagonist; Chwalisz, K. *et al., Prenat. Neonat. Med.* (1996), Vol. 1, pp. 292-329, which discusses the induction of abortion, in combination with an antiprogestin and in further combination with a prostaglandin, and the control and management of labor and delivery; and Chwalisz, K. *et al., Hum. Reprod.* (1997), vol. 12, pp. 101-109, which discusses the treatment of cervical incompetence, alone or in combination with progesterone or a progestin.

Those skilled in the art will also recognize that the compounds of the present invention include 1-substituted imidazoles. This class of compounds has previously been described as mechanism-based, heme-binding inhibitors of the cytochrome P450 family of enzymes (Maurice, M. *et al., FASEB J.* (1992), Vol. 6, pp. 752-8) in addition to nitric oxide synthesis (Chabin, R.NM. *et al., Biochemistry* (1996), Vol. 35, pp. 9567-9575). The compounds of the present invention may thus be useful as inhibitors of selected cytochrome P450 family members of therapeutic interest including, but not limited to, P450 enzymes involved in steroid and retinoid biosynthesis (Masamura *et al., Breast Cancer Res. Treat.* (1995), Vol. 33, pp. 19-26; Swart, P. *et al., J. Clin. Endocrinol. Metab.*, Vol. 77, pp. 98-102; Docks, P. *et al., Br. J. Dermatol.* (1995), Vol. 133, pp. 426-32) and cholesterol biosynthesis (Burton, P.M. *et al., Biochem. Pharmacol.* (1995), Vol. 50, pp. 529-544; and Swinney, D.C. *et al., Biochemistry* (1994), Vol. 33, pp. 4702-4713). Imidazole-based compounds may also have antifungal activity (Aoyama, Y. *et al., Biochem. Pharmacol.* (1992), Vol. 44, pp. 1701-1705). The P450 inhibitory activity of the compounds of the present invention can be assessed using appropriate assay systems specific for the P450 isoform of interest. Such assays are included in the references cited above. One additional example of mammalian cytochrome P450 isoform that may be inhibited by the compounds of the present invention is cytochrome P450 3A4 which can be assayed in a manner similar to the method described in Yamazaki *et al., Carcinogenesis* (1995), Vol. 16, pp. 2167-2170.

Testing of the Compounds of the Invention

Nitric oxide synthases are complex enzymes that catalyze the conversion of L-arginine to nitric oxide (NO) and citrulline. Catalysis proceeds through two successive oxidations of the guanidinium group of L-arginine.

A cell-based nitric oxide synthase assay employing the measurement of nitric oxide oxidation product, nitrite, in the conditioned medium of cultured cells was employed for the

evaluation of the compounds of the invention. The murine monocytic cell lines RAW 264.7 and J774 are well documented as capable of producing >10 μM nitrite in response to immunostimulation:

Induction of iNOS in RAW 264.7 Mouse Monocytes

RAW 264.7 murine macrophage cells were obtained from American Type Culture Collection (Rockville, Maryland) and were maintained in RPMI 1640 containing 10% fetal bovine serum (FBS), 5000 units/mL of penicillin and streptomycin, and 2mM glutamine (maintenance medium). NOS activity was measured by a fluorescent assay of the nitric oxide oxidation product, nitrite, (Diamani *et al.*, *Talanta* (1986), Vol. 33, pp. 649-652). Induction of iNOS (inducible nitric oxide synthase) is stimulated by treatment of the cells with lipopolysaccharide and γ-interferon. The method of the assay is described below.

Cells are harvested, diluted to 500,000 cells/mL with maintenance medium, and seeded into 96-well plates at 100 μl/well. The plates are incubated overnight at 37°C, under a 5% CO_2 atmosphere. The medium is then replaced with 90 μl of BME medium containing 10% FBS, 100 units/mL of penicillin, 100 μl streptomycin, 2 mM glutamine, 100 units/mL of interferon-γ and 2 μg/mL of lipopoly-saccharide. *N*-guanidino-methyl-L-arginine is added to four wells (negative control) at a final concentration of 200 μM using 10 μl of 2 mM stock solution in 100 mM Hepes, pH 7.3 + 0.1% DMSO and four wells receive only the 100 mM Hepes/0.1% DMSO buffer (positive control). Compounds for evaluation are dissolved at 10-fold the desired final concentration in Hepes/DMSO and 10 μL of these solutions is transferred to the 96-well plate. The plates are incubated for 17 hrs at 37°C, under a 5% CO_2 atmosphere. Nitrite accumulated in the culture medium is determined as follows: add 15 μL of 2,3-diaminonaphthalene (10 μg/mL in 0.75 M HCl) to each well and incubate for 10 minutes at room temperature. Add 15 μl of 1 N NaOH and measure the fluorescence emission at 405 nm, using an excitation wavelength of 365 nm. Enzyme activity in experimental wells is normalized to percent control using the positive and negative control values. The signal to noise ratio is >10 for the assay.

The compounds of the invention, when tested in this assay, demonstrated the ability to inhibit nitric oxide production.

Various *in vivo* assays may be employed to determine the efficacy of the compounds of the invention in treating a condition resulting from an abnormality in nitric oxide production, such as arthritis. The following is a description of such an assay utilizing rats:

Effects of Compounds of the Invention on Adjuvant-Induced Arthritis in Rats

Male Lewis rats were injected intradermally (proximal quarter of the tail) with 0.1 mL of Mycobacterium butyricum in Incomplete Freund's Adjuvant (10 mg/mL). Either vehicle (acidified saline, 1 mL/kg) or a compound of the invention (3, 10, or 30 mg/kg) were administered subcutaneously (b.i.d.), starting on the day following adjuvant immunization, and continued until the end of the experiment (N= 10 rats per treatment group). Clinical scores (see below) were measured in all limbs 3 times per week throughout the study. Rats were euthanized 34-35 days

after immunization. At the time of euthanasia, a radiologic evaluation (see below) of the hind paws was performed, a blood sample was collected for clinical blood chemistry and drug levels (high dose group only; 6 or 12 hours post final dose), a section of liver was obtained for measurement of potential toxicity, and the hind limbs were preserved for histopathological determination.

Clinical scoring - each limb was graded according to the following scale:

0	no signs of inflammation
1	moderate redness, first indication of swelling, joint flexible
2	moderate redness, moderate swelling, joint flexible
3	redness, significant swelling and distortion of the paw, joint beginning to fuse
4	redness, gross swelling and distortion of the paw, joint completely fused

Radiological scoring - each hind limb was graded on a scale of 0-3 for each of the following parameters:

soft tissue swelling
cartilage loss
erosion
heterotropic ossification

The compounds of the invention, when tested in this assay, demonstrated the ability to treat the arthritis present in the rats.

Those skilled in the art will also recognize that numerous assays for the activity of the NOS isoforms (iNOS, nNOS and eNOS) exist which can be used to evaluate the biological activity of the compounds of the current invention. These include assays for native NOS isoforms in tissues studied *ex vivo* (Mitchell *et al., Br. J. Pharmacol.* (1991), Vol. 104, pp. 289-291; Szabo *et al., Br. J. Pharmacol.* (1993), Vol. 108, pp. 786-792; Joly *et al., Br. J. Pharmacol.* (1995), Vol. 115, pp. 491-497) as well as primary cell cultures and cell lines (Forstermann *et al., Eur. J. Pharmacol.* (1992), Vol. 225, pp. 161-165; Radmoski *et al., Cardiovasc. Res.* (1993), Vol. 27, pp. 1380-1382; Wang *et al., J. Pharmacol. Exp. Ther.* (1994), Vol. 268, pp. 552-557). Those skilled in the art will also recognize that recombinant NOS enzymes can be expressed in heterologous cells by either transient transfection (Karlsen *et al., Diabetes,* (1995), Vol. 44, pp. 753-758), stable transfection (McMillan *et al., Proc. Natl. Acad. Sci.* (1992), Vol. 89, pp. 11141-11145; Sessa *et al., J. Biol. Chem.* (1995), Vol. 270, pp. 17641-17644) or *via* the use of lytic virus transfection (Busconi & Michel, *Mol. Pharmacol.* (1995), Vol. 47, pp. 655-659; List *et al., Biochem. J.* (1996), Vol. 315, pp. 57-63) using NOS cDNAs. Heterologous expression can be achieved in mammalian cells (McMillan *et al., Proc. Natl. Acad. Sci.* (1992), Vol. 89, pp. 11141-11145), insect cells (Busconi & Michel, *Mol. Pharmacol.* (1995), Vol. 47, pp. 655-659; List *et al., Biochem. J.* (1996), Vol. 315, pp. 57-63), yeast (Sari *et al., Biochemistry* (1996), Vol. 35, pp.

7204-7213) or bacteria (Roman *et al., Proc. Natl. Acad. Sci.* (1995), Vol. 92, pp. 8428-8432; Martasek *et al., Biochem. Biophys. Res. Commun.* (1996), Vol. 219, pp. 359-365). Any of these heterologous expression systems can be used to establish iNOS, nNOS and eNOS assay systems to evaluate the biological activity of the compounds of the present invention.

Administration of the Compounds of the Invention

Any suitable route of administration may be employed for providing a patient with an effective dosage of compounds of the invention. For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, and like forms of administration may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions of the present invention comprise the compounds of the invention as the active ingredient, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations. Methods for their preparation are well known in the art.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled or sustained release means and delivery devices.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

Preferred Embodiments

Of the compounds of formula (Ya), formula (Yb) and formula (Yc) as described above in the Summary of the invention, a preferred group of compounds are those compounds having the formula (Yc) wherein n is 1; m is 2 or 3; A is $-C(O)OR^1$ or $-C(O)N(R^1)R^2$; each W is CH; R^1 is hydrogen or alkyl; and R^2 is hydrogen, alkyl, $-(CH)_n-N(R^1)_2$, optionally substituted

heterocyclylalkyl or optionally substituted aralkyl.

Of this subgroup of compounds, a preferred class of compounds are those compounds wherein R^4 is $-N(R^1)R^2$ where R^1 is hydrogen or alkyl and R^2 is heterocyclylalkyl selected from the group consisting of (1,3-benzodioxol-5-yl)methyl or (1,4-benzodioxan-6-yl)methyl.

Of this class of compounds, preferred compounds are selected from the group consisting of:

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid, ethyl ester;

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N,N*-diethylacetamide;

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-(2-dimethylaminoethyl)acetamide;

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide;

2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N,N*-diethylacetamide;

2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-methylacetamide;

2-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-methylacetamide;

2-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N,N*-diethylacetamide;

2-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide; and

2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide.

Of the preferred subgroup of compounds, a preferred class of compounds are those compounds wherein R^4 is heterocyclyl.

Of this class of compounds, preferred compounds are selected from the group consisting of:

2-[[pyridin-3-ylmethyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(*1H*-imidazol-1-yl)-6-methylpyrimidin-4-yl][(1,3-benzodioxol-5-yl)methyl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide; and

2-[[2-(*1H*-imidazol-1-yl)-6-methylpyrimidin-4-yl][2-(morpholin-4-yl)ethyl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide.

Of this subgroup of compounds, another preferred class of compounds are those compounds wherein R^4 is hydroxy, cyano, $-N(R^1)R^2$, $-N(R^1)$-C(O)-R^1, $-N(R^1)$-C(O)OR^1, $-N(R^1)$-

$S(O)_t$-R^1, or -$N(R^1)$-C(O)-$N(R^1)_2$, where each R^1 and each R^2 is independently hydrogen, alkyl or aralkyl.

Of this class of compounds, preferred compounds are selected from the group consisting of:

2-[[3-hydroxypropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-cyanoethyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(di(phenylmethyl)amino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(ureido)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

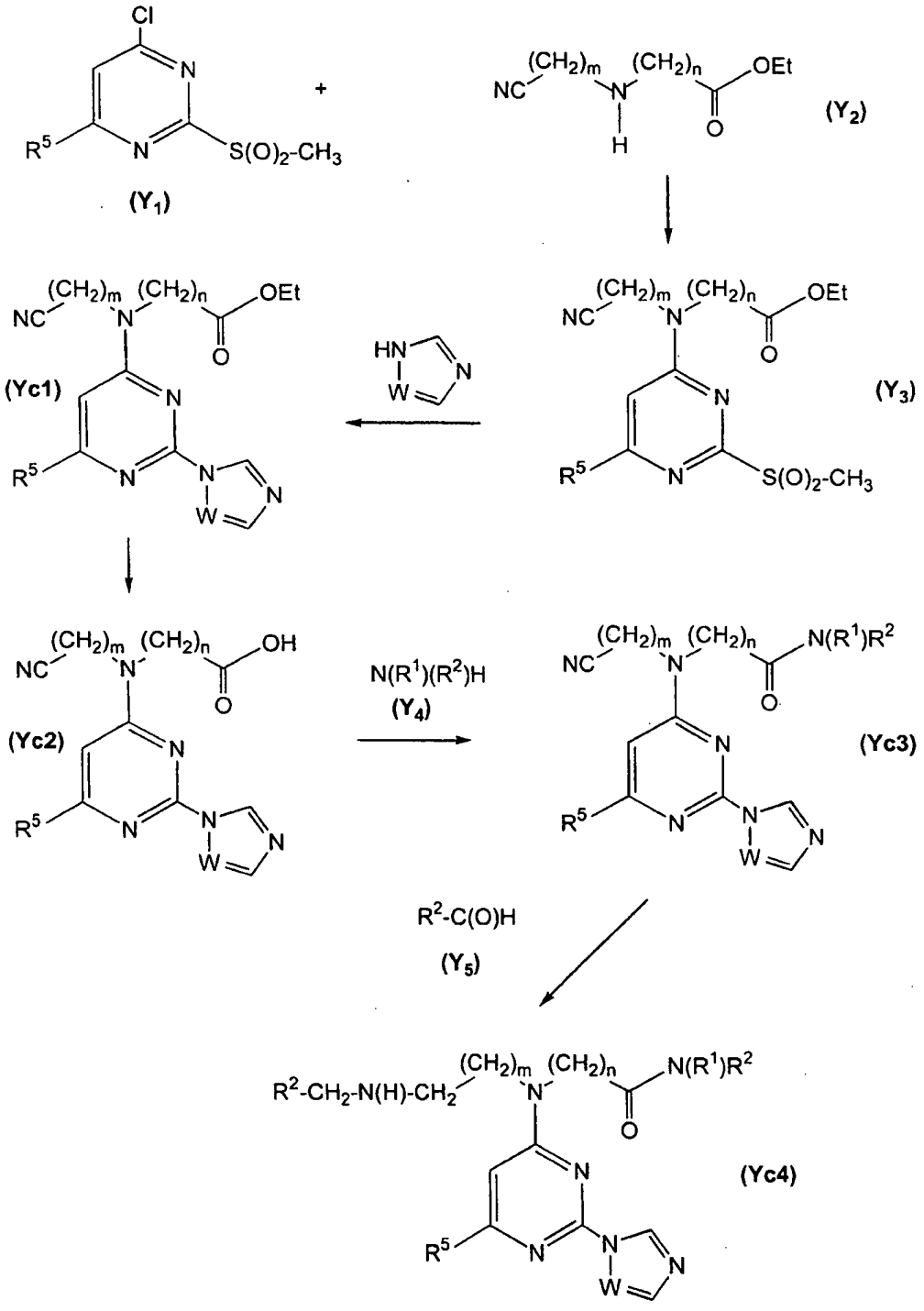
2-[[3-(ureido)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; and

2-[[3-(ureido)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide.

Preparation of the Compounds of the Invention

Reaction Schemes 1 through 4 depict methods of preparing compounds of formula (Yc). Compounds of formula (Ya) and formula (Yc) may be similarly prepared:

Reaction Scheme 1



Compounds of formulae (Y_1), (Y_2), (Y_4) and (Y_5) are commercially available or may be prepared by methods disclosed herein or by methods known to those of ordinary skill in the art. Each R^1, R^2, m and n are independently as described above in the Summary of the Invention for compounds of formula (Ya), formula (Yb) and formula (Yc); and R^5 and W are also as described above in the Summary of the Invention for compounds of formula (Ya), formula (Yb) and formula (Yc).

The above synthesis may be carried out as follows:

To *N*-cyanoethylglycine, ethyl ester (15.9 g, 102 mmol) (a compound of formula (Y_2)) dissolved in DMSO (70 mL) was added 4-chloro-6-methyl-2-methylsulfonylpyrimidine (18.8 g, 91 mmol) (a compound of formula (Y_1)) and diisopropylethylamine (18 mL, 100 mmol). After stirring for 16 hours, the reaction temperature was raised to 70°C and imidazole (26.5 g, 0.39 mol) was added. After stirring for 1 day, the reaction was cooled to ambient temperature and added to ice water. The solid that formed was suction filtered and collected on paper to give 9.9 g of 2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid, ethyl ester (a compound of formula (Yc1)).

To 2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid, ethyl ester (4.51 g, 14.4 mmol) dissolved in THF (250 mL) was added LiOH (0.91 g, 21.7 mmol) and water (30 mL). After stirring for 18 hours, most of the solvent was removed in vacuo and 1 N HCl (21.7 mL, 21.7 mmol) was added. The solid that formed was suction filtered and collected on paper to give 3.17 g of 2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid (a compound of formula (Yc2)).

To 2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid (1.53 g, 5.3 mmol) slurried in DMF (25 mL) was added carbonyldiimidazole (0.87 g, 5.4 mmol). After stirring for 2 hours, diethylamine (1.0 mL, 9.7 mmol) (a compound of formula (Y_4)) was added. After stirring for 18 hours, the reaction was partitioned with ethyl acetate and water. The organic layer was separated, dried (Na_2SO_4), and the solvent was removed in vacuo to give 0.91 g of 2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*,*N*-diethylacetamide (a compound of formula (Yc3)).

The following compounds of formula (Yc3) and derivatives thereof were prepared in a similar manner with the appropriately substituted starting materials:

2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-methylacetamide;

2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide.

Ammonia (g) was bubbled into 2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*,*N*-diethylacetamide (0.22 g, 0.65 mmol) dissolved in MeOH (25 mL). Raney Nickel (0.8 g) was added and the mixture was placed under nitrogen at 50 psi. When the reaction was determined to be complete by TLC, the reaction mixture was suction filtered through celite and

the solvent was removed in vacuo. To the residue dissolved in MeOH (10 mL) was added piperonal (0.29 g, 1.9 mmol) and $NaBH(OAc)_3$ (0.40 g, 1.9 mmol). After stirring for 18 hours, the solvent was evaporated and the residue was partitioned between ethyl acetate and aqueous bicarbonate solution. The organic layer was separated, dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography on silica with acetonitrile/ammonium hydroxide (19/1) gave 2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N,N*-diethylacetamide, a compound of formula (Yc4); NMR ($CDCl_3$) 8.4 (s, 1), 7.65 (s, 1), 7.0 (s, 1), 6.85 (s, 1), 6.75 (d, 1), 6.5 (d, 1), 6.05 (br, 1), 5.85 (s, 2), 4.3 (s, 2), 3.85 (s, 2), 3.65 (br, 2), 3.4 (m, 4), 2.95 (t, 2), 2.3 (s, 3), 2.2 (m, 2), 1.25 (t, 3), 1.1 (t, 3) ppm.

The following compounds of formula (Yc4) and derivatives thereof were prepared in a similar manner with appropriately substituted starting materials:

2-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-methylacetamide; NMR ($CDCl_3$) 8.5 (s, 1), 7.8 (s, 1), 7.1 (s, 1), 6.75 (m, 3), 6.25 (br, 1), 4.25 (s, 4), 4.15 (br, 2), 3.7 (s, 2), 3.6 (s, 2), 2.8 (d, 3), 2.75 (m, 2), 2.4 (s, 3), 1.85 (m, 2) ppm;

2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-methylacetamide; NMR ($DMSO-d_6$) 8.4 (s, 1), 8.0 (m, 1), 7.8 (s, 1), 7.05 (s, 1), 6.9 (s, 1), 6.8 (m, 2), 6.65 (s, 1), 6.3 (br, 1), 5.95 (s, 2), 4.1 (br, 2), 3.6 (s, 2), 3.55 (br, 2), 3.3 (br, 3), 2.6 (m, 2), 2.3 (s, 3), 1.75 (m, 2) ppm;

2-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N,N*-diethylacetamide; NMR ($CDCl_3$) 8.4 (s, 1), 7.7 (s, 1), 7.05 (s, 1), 6.85 (s, 1), 6.6 (m, 2), 6.3 (br, 1), 4.4 (s, 2), 4.25 (s, 4), 3.7 (s, 2), 3.6 (m, 2), 3.4 (q, 4), 2.7 (t, 2), 2.35 (s, 3), 1.9 (m, 2), 1.35 (t, 3), 1.15 (t, 3) ppm;

2-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide; NMR ($CDCl_3$) 8.5 (s, 1), 7.8 (s, 1), 7.1 (s, 1), 6.75 (m, 3), 6.3 (br, 1), 6.0 (br, 1), 4.2 (s, 4), 4.15 (s, 2), 3.65 (m, 4), 2.75 (m, 2), 2.4 (s, 3), 1.85 (m, 2) ppm;

2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide; NMR ($CDCl_3$) 8.5 (s, 1), 7.75 (s, 1), 7.05 (s, 1), 6.75 (m, 3), 6.3 (br, 1), 5.95 (s, 2), 5.4 (br, 1), 4.15 (s, 2), 3.7 (br, 2), 3.6 (s, 2), 2.75 (t, 2), 2.4 (s, 3), 1.85 (m, 2) ppm.

Compounds of formula (Y_4) wherein R^2 is 2-(1,4-benzodioxan-6-yl)ethyl may be prepared as follows and reacted with the compound of formula (Yc2) to prepare compounds of formula (Yc3), which may be further reacted as described above to form compounds of formula (Yc4):

To 1,4-benzodioxane-6-carboxaldehyde (10.0 g, 60 mmol) in acetic acid (50 mL) was added nitromethane (6.3 mL, 1.9 eq.) and ammonium acetate (5.1 g, 1.1 eq.). After heating at 110°C for 4 hours the mixture was cooled to ambient temperature, water (150 mL) was added, and the solid precipitate was collected by filtration. The solid was crystallized from methylene chloride-hexane (1:1, 45 mL) to obtain 7.6 g (61 %) of 6-(2-nitroethenyl)-1,4-benzodioxane. To a

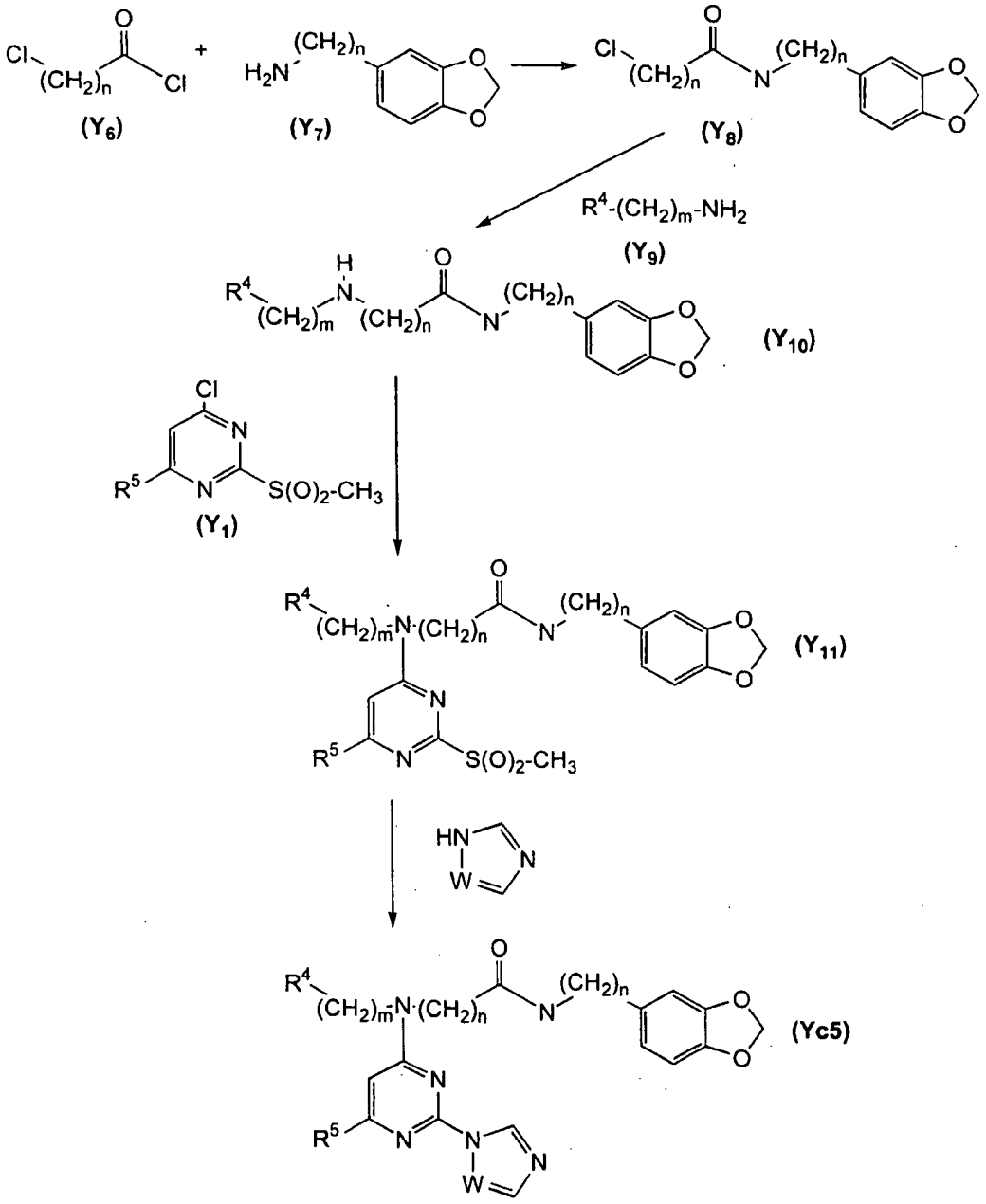
portion of the solid (3.58 g) dissolved in MeOH-EtOH-AcOEt (1:1:1, 450 mL) was added 10% Pd/C (1.7 g) and concentrated HCl (3.3 mL, 2.3 eq). After shaking on a Parr hydrogenator at 45 psi for 5 hours, the catalyst was removed by filtration through Celite and washed with methanol. Evaporation of the filtrate gave 3.59 g (96%) of 1,4-benzodioxan-6-ethanamine, hydrochloride.

Alternatively, compounds of formula (Y_3) may be reacted as follows to form compounds of formula (Yc3) wherein R^1 and R^2 are both hydrogen, which may be further reacted with a compound of formula (Y5) to form compounds of formula (Yc4):

To 2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid, ethyl ester (2.3 g, 7.3 mmol) slurried in MeOH (50 mL) and cooled in a dry ice/acetone bath was bubbled NH_3. The bomb was sealed and heated in an oil bath at 65°C for 2 days. The reaction was cooled in a dry ice/acetone bath and the seal was broken. The solid was suction filtered to give 1.7 g of 2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide.

Reaction Scheme 2 depicts another method of preparing compounds of formula (Yc). Compounds of formula (Ya) and formula (Yb) may be similarly prepared:

Reaction Scheme 2



Compounds of formulae (Y_1), (Y_6), (Y_7), (Y_9) and (Y_5) are commercially available or may be prepared by methods disclosed herein or by methods known to those of ordinary skill in the art. Each R^1, R^2, m and n are independently as described above in the Summary of the Invention for compounds of formula (Ya), formula (Yb) and formula (Yc); and R^4, R^5 and W are also as described above in the Summary of the Invention for compounds of formula (Ya), formula (Yb) and formula (Yc).

The above synthesis may be carried out as follows:

To homopiperonylamine hydrochloride (2.14 g, 10.6 mmol) (a compound of formula (Y_7)) in CH_2Cl_2 (20 mL) in an ice bath was added triethylamine (3.1 mL, 21 mmol) and chloroacetyl chloride (0.85 mL, 10 mmol) (a compound of formula (Y_6)) . After warming to ambient temperature and stirring for 16 hours, the reaction was partitioned with 1 N HCl. The organic layer was separated, washed with aqueous bicarbonate, dried (Na_2SO_4), and the solvent was removed in vacuo to give 1.8 g of 2-chloro-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide, a compound of formula (Y_8).

To 2-chloro-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide (0.45 g, 1.9 mmol) in ethanol (10 mL) was added 3-aminopropanol (0.72 mL, 9.4 mmol) (a compound of formula (Y_9)). After heating the reaction in an oil bath at 60°C for 1 day, the reaction was partitioned with ethyl acetate and water. The organic layer was separated, washed with brine, dried (Na_2SO_4), and the solvent was removed in vacuo to give 0.44 g of 2-[(3-hydroxypropyl)amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide, a compound of formula (Y_{10}).

The following compounds of formula (Y_{10}) were prepared in a similar manner from the appropriately substituted starting materials:
2-[(3-pyridinylmethyl)amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;
2-[[2-(4-morpholinyl)ethyl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;
2-[(1,3-benzodioxol-5-ylmethyl)amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide.

To 2-[(3-hydroxypropyl)amino]-*N*-(1,3-benzodioxol-5-ylmethyl)acetamide (0.44 g, 1.6 mmol) dissolved in DMSO (5 mL) was added 4-chloro-6-methyl-2-methylsulfonylpyrimidine (0.31 g, 1.5 mmol) (a compound of formula (Y_1) and diisopropylethylamine (0.55 mL, 3.1 mmol). After stirring for 16 hours, the reaction temperature was raised to 70°C and imidazole (0.47 g, 6.9 mol) was added. After stirring for 1 day, the reaction was cooled to ambient temperature and partitioned with water and ethyl acetate. The organic layer is separated, dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography on silica with CH_2Cl_2/MeOH gave 2-[[3-hydroxypropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide, a compound of formula (Yc5).

The following compounds of formula (Yc5) and derivatives thereof were prepared in a similar manner with the appropriately substituted starting materials:

2-[[pyridin-3-ylmethyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.6 (s, 1), 8.45 (s, 2), 8.15 (t, 1), 7.8 (s, 1), 7.7 (d, 1), 7.35 (br, 1), 7.05 (s, 1), 6.8 (br, 2), 6.6 (br, 2), 6.0 (s, 2), 4.8 (m, 2), 4.2 (m, 2), 3.3 (m, 2), 2.6 (m, 2), 2.3 (s, 3) ppm;

2-[[2-cyanoethyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide; NMR($CDCl_3$) 8.5 (s, 1), 7.8 (s, 1), 7.1 (s, 1), 6.6 (d, 1), 6.55 (d, 1), 6.3 (t, 1), 6.2 (s, 1), 5.9 (s, 2), 4.2 (s, 2), 3.9 (t, 2), 3.55 (t, 2), 2.8 (t, 2), 2.75 (t, 2), 2.45 (s, 3) ppm;

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid, ethyl ester; NMR ($CDCl_3$) 8.5 (s, 1), 7.8 (s, 1), 7.05 (s, 1), 6.85 (s, 1), 6.75 (m, 2), 6.4 (br, 1), 5.9 (s, 2), 4.2 (m, 4), 3.6 (m, 2), 3.4 (s, 2), 2.4 (t, 2), 2.35 (s, 3), 2.2 (s, 3), 1.9 (t, 3), 1.2 (t, 3) ppm;

2-[[2-(*1H*-imidazol-1-yl)-6-methylpyrimidin-4-yl][2-(morpholin-4-yl)ethyl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.5 (s, 1), 7.8 (s, 1), 7.1 (s, 1), 6.5 (d, 1), 6.3 (br, 1), 6.15 (s, 2), 5.7 (br, 2), 4.0 (m, 4), 3.45 (m, 8), 2.6 (m, 2), 2.4 (s, 3), 2.35 (m, 4) ppm; and

2-[[2-(*1H*-imidazol-1-yl)-6-methylpyrimidin-4-yl][(1,3-benzodioxol-5-yl)methyl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.75 (s, 1), 8,15 (t, 1), 7.8 (s, 1), 7.15 (s, 1), 6.75 (d, 1), 6.7 (m, 2), 6.55 (d, 1), 6.4 (m, 2), 6.2 (br, 1), 6.0 (s, 2), 5.9 (s, 2), 4.65 (br, 2), 4.1 (br, 2), 3.4 (m, 2), 2.3 (s, 3) ppm.

Alternatively, compounds of formula (Y_{10}) and derivatives thereof are prepared as follows:

In a manner similar to the preparation of compounds of formula (Yc3) above, to 2-[(2-cyanoethyl)(dimethylethoxycarbonyl)amino]acetic acid (8.3 g, 39 mmol) dissolved in CH_2Cl_2 (100 mL) was added carbonyldiimidazole (6.2 g, 38 mmol). After stirring for 30 minutes, homopiperonylamine, hydrochloride (8.0 g, 41 mmol) and diisopropylethylamine (7.5 mL, 43 mmol) were added. After stirring for 18 hours, most of the solvent was removed in vacuo and the residue was partitioned with ethyl acetate and 1N HCl. The organic layer was separated, washed with aqueous bicarbonate and brine, dried (Na_2SO_4), and the solvent was removed in vacuo to give 13 g of 2-[(2-cyanoethyl)(dimethylethoxycarbonyl)amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide.

To 2-[(2-cyanoethyl)(dimethylethoxycarbonyl)amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide (14 g, 37 mmol) in CH_2Cl_2 (75 mL) cooled in an ice bath was added trifluoroacetic acid (50 mL). After stirring for 1 hour the ice bath was removed and the solvent was removed in vacuo. The residue was triturated with ether and a solid formed. The solid was collected by filtration to give 12 g of 2-[(2-cyanoethyl)amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide, trifluoroacetic acid salt, a compound of formula (Y_{10}).

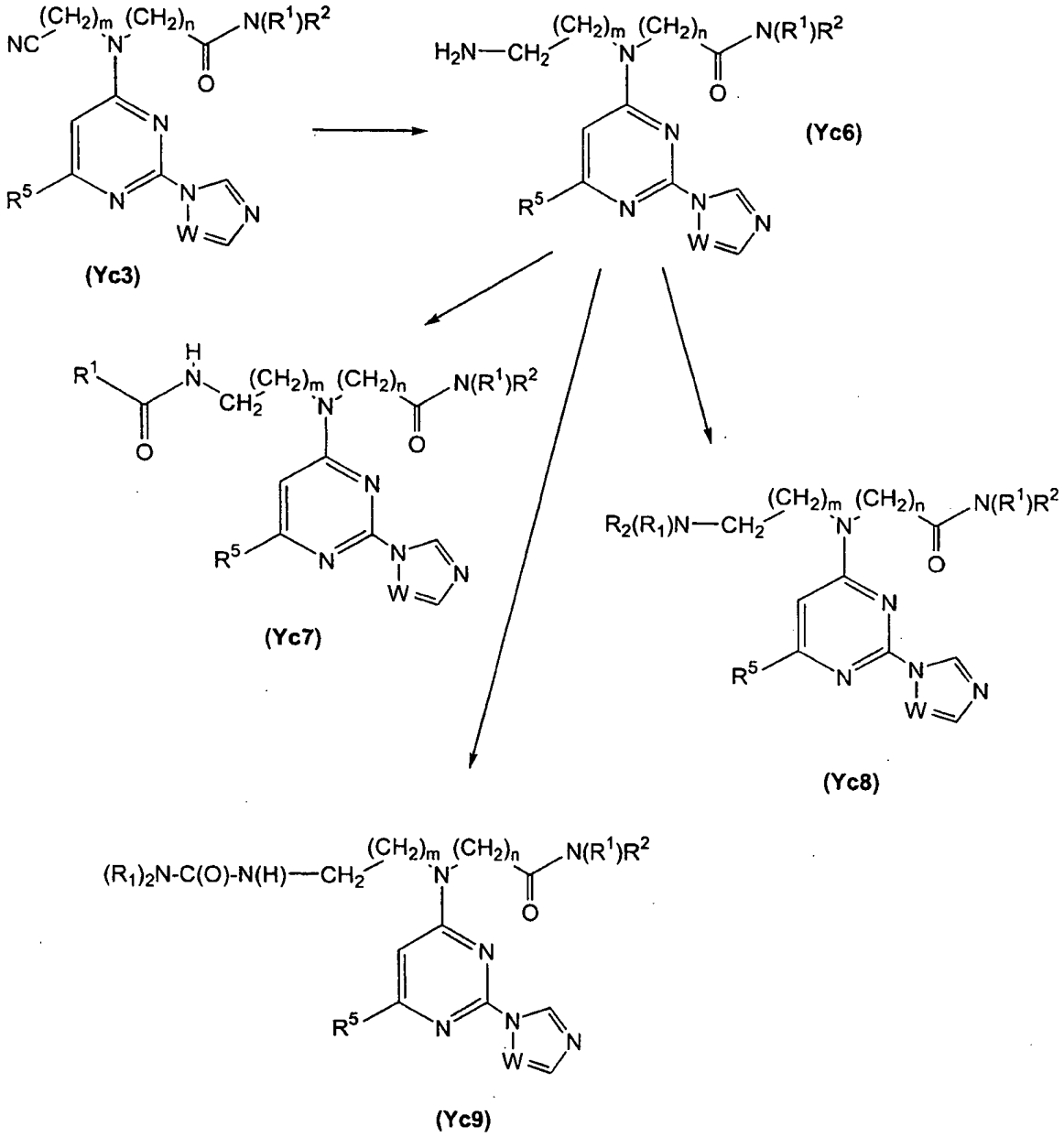
Alternatively, compounds of formula (Y_{10}) and derivatives thereof are prepared as follows:

To *N*-methyl-β-alaninenitrile (50 g, mmol in acetonitrile was added piperonyl chloride (50 g, mmol). After stirring for 18 h, the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2, washed with aqueous carbonate, dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was dissolved in methanol saturated with ammonia (600 mL) and Raney nickel (10 g) was added. After shaking under an atmosphere of hydrogen at 20 psi for 6 h, the reaction was filtered through celite and the solvent was removed in vacuo to give 65 g of *N*-(1,3-benzodioxol-5-ylmethyl)-*N*-methyl-1,3-propanediamine.

To *N*-(1,3-benzodioxol-5-ylmethyl)-*N*-methyl-1,3-propanediamine (33 g, 0.15 mol) in CH_2Cl_2 (500 mL) was added ethyl glyoxalate (30 mL of a 50% toluene solution, 0.15 mol) and sodium triacetoxyborohydride (40 g, 0.19 mol). After stirring for 4 hours, the reaction was washed with aqueous potassium carbonate and the solvent removed in vacuo. Chromatography on silica with CH_2Cl_2/ MeOH/ ammonium hydroxide gave 14 g of 2-[[3-[(1,3-benzodioxol-5-ylmethyl)amino]propyl]amino]acetic acid, ethyl ester, a compound of formula (Y_{10}).

Reaction Scheme 3 depicts another method of preparing compounds of formula (Yc). Compounds of formula (Ya) and formula (Yb) may be similarly prepared with the appropriately substituted starting materials.

Reaction Scheme 3



(Yc3) (Yc6) (Yc7) (Yc8) (Yc9)

Compounds of formulae (Yc3) are prepared by methods disclosed herein. Each R^1, R^2, m and n are independently as described above in the Summary of the Invention for compounds of formula (Ya), formula (Yb) and formula (Yc); and R^5 and W are also as described above in the Summary of the Invention for compounds of formula (Ya), formula (Yb) and formula (Yc).

The above synthesis may be carried out as follows:

To 2-[(2-cyanoethyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide (2.5 g, 5.8 mmol) (a compound of formula (Yc3)) in MeOH (50 mL) was bubbled ammonia. Raney nickel (1.0 g of a 50 % slurry) was added and the reaction

was placed on a Parr hydrogenator at 50 psi. After shaking for 16 hours, the pressure was released and the reaction mixture was suction filtered through Celite. The solvent was removed in vacuo and the residue was chromatographed on silica gel (9:1 CH_3CN/NH_4OH) to afford 2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide, a compound of formula (Yc6); as a white solid; NMR (DMSO-d_6, 90°C) 8.4 (s, 1), 7.8 (s, 1), 7.0 (s, 1), 6.75 (d, 1), 6.7 (s, 1), 6.6 (d, 1), 5.9 (s, 2), 4.1 (s, 2), 3.6 (br, 2), 3.3 (m, 2), 2.75 (t, 2), 2.6 (t, 2), 2.3 (s, 3), 1.8 (m, 2) ppm.

The following compounds of formula (Yc6) and derivatives thereof were prepared in a similar manner with appropriately substituted starting materials:

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide; NMR (DMSO-d_6, 90 C) 8.4 (s, 1), 7.8 (s, 1), 7.05 (m, 3), 6.75 (d, 2), 6.45 (s, 1), 4.1 (s, 2), 3.7 (s, 3), 3.55 (t, 2), 3.3 (m, 2), 3.2 (s, 2), 3.6 (m, 4), 2.3 (s, 3) ppm;

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; NMR (DMSO-d_6) 8.42 (br, 1), 8.08 (br, 1), 7.80 (br, 1), 7.02 (s, 1), 6.65 (m, 4), 4.16 (m, 6), 4.05 (br, 1), 3.65 (br, 1), 3.45 (br, 2), 3.15 (br, 2), 2.59 (m, 4), 2.35 (s, 3), 1.62 (m, 2) ppm; and

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.46 (s, 1), 7.75 (s, 1), 7.06 (s, 1), 6.80 (s, 1), 6.70 (d, 1), 6.52 (d, 1), 6.18 (br, 1), 4.46 (t, 2), 4.06 (br, 2), 3.60 (br, 2), 3.45 (m, 2), 3.05 (m, 2), 2.78 (br, 2), 2.65 (m, 2), 2.39 (s, 3), 1.70 (br, 4) ppm.

Compounds of formula (Yc6) may be used to prepare compounds of formula (Yc7), (Yc8) and (Yc9) as set forth below:

To 2-[(3-aminopropyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide (0.3 g, 0.7 mmol) (a compound of formula (Yc6)) dissolved in MeOH (10 mL) was added formalin (0.15 mL, 2.0 mmol) and sodium triacetoxyborohydride (0.37 g, 1.7 mmol). After stirring for 16 hours, the solvent was removed in vacuo. The residue was partitioned with ethyl acetate and aqueous bicarbonate. The organic layer was separated, washed with brine, dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography on silica with acetonitrile/ammonium hydroxide gave 0.14 g of 2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide, a compound of formula (Yc8); NMR ($CDCl_3$) 8.5 (s, 1), 7.8 (s, 1), 7.1 (s, 1), 6.5 (d, 1), 6.45 (s, 2), 6.4 (d, 1), 6.2 (m, 1), 5.9 (s, 2), 4.15 (s, 2), 3.55 (m, 2), 3.5 (q, 2), 2.6 (t, 2), 2.4 (s, 3), 2.3 (t, 2), 2.25 (s, 6), 1.7 (m, 2) ppm.

To 2-[(3-aminopropyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide (50 mg, 0.11 mmol) (a compound of formula (Yc6)) in methanol (2 mL) was added benzaldehyde (0.2 M in methanol, 68 µL, 0.14 mmol). After stirring for 15 minutes, borane-pyridine complex (0.2 M in methanol, 0.14 mmol) was added. After 2 hours, the

solution was evaporated. The residue was partitioned into water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. The combined ethyl acetate fractions were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (2:1 ethyl acetate/hexanes) to provide 2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide, a compound of formula (Yc8); as a white solid; NMR ($CDCl_3$) 8.65 (s, 1), 7.7 (s, 1), 7.2 (br, 5), 7.1 (s, 1), 6.6 (d, 1), 6.55 (s, 1), 6.5 (d, 1), 6.1 (br, 2), 5.9 (s, 2), 3.95 (br, 2), 3.5 (br, 6), 2.7 (m, 3), 2.35 (s, 6) ppm.

The following compounds of formula (Yc8) and derivatives thereof were prepared in a similar manner with appropriately substituted starting materials:

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.75 (s, 1), 7.2 (br, 5), 7.05 (s, 1), 6.9 (d, 2), 6.65 (d, 2), 6.4 (br, 1), 4.1 (s, 2), 3.75 (s, 2), 3.7 (s, 3), 3.6 (br, 2), 3.45 (dd, 2), 2.7 (m, 4), 2.35 (s, 3), 1.8 (s, 2) ppm;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.75 (s, 1), 7.05 (s, 1), 6.85 (d, 2), 6.6 (d, 2), 6.3 (br, 1), 6.25 (br, 1), 4.1 (s, 2), 3.7 (s, 3), 3.5(m, 4), 2.7 (t, 2), 2.4 (s, 3), 2.3 (t, 2), 2.2 (s, 6), 1.75 (m, 2) ppm;

2-[[3-(di(phenylmethyl)amino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.70 (s, 1), 7.35 (m, 10), 7.04 (s, 1), 6.62 (d, 1), 6.45 (s, 1), 6.40 (d, 1), 6.06 (br, 1), 5.96 (br, 1), 4.15 (br, 4), 3.92 (br, 2), 3.60 (s, 4), 3.45 (m, 4), 2.62 (t, 2), 2.50 (t, 2), 2.30 (s, 3), 1.72 (m, 2) ppm;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.75 (s, 1), 7.25 (m, 6), 7.05 (s, 1), 6.60 (d, 1), 6.45 (s, 1), 6.40 (d, 1), 6.20 (br, 1), 4.10 (m, 6), 3.70 (br, 4), 3.40 (m, 2), 2.65 (t, 2), 2.60 (t, 2), 2.40 (s, 3), 1.90 (br, 1), 1.76 (m, 2) ppm;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.75 (s, 1), 7.05 (s, 1), 6.65 (d, 1), 6.50 (s, 1), 6.42 (s, 1), 6.30 (t, 1), 6.16 (br, 1), 4.12 (m, 6), 3.50 (m, 4), 2.75 (m, 2), 2.62 (t, 2), 2.56 (s, 6), 2.40 (s, 3), 2.10 (m, 2) ppm;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.46 (s, 1), 7.75 (s, 1), 7.30 (m, 6), 7.10 (s, 1), 6.82 (s, 1), 6.68 (d, 1), 6.54 (d, 1), 6.25 (br, 1), 4.46 (t, 2), 4.10 (br, 2), 3.70 (br, 2), 3.62 (br, 2), 3.45 (m, 2), 3.05 (t, 2), 2.65 (m, 4), 2.40 (s, 3), 1.78 (m, 2) ppm; and

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.76 (s, 1), 7.06 (s, 1), 6.85 (s, 1), 6.70 (d, 1), 6.50 (d, 1), 6.16 (br, 2), 4.50 (t, 2), 4.10 (s, 2), 3.52 (m, 4), 3.05 (t, 2), 2.76 (m, 2), 2.68 (m, 2), 2.62 (s, 6), 2.42 (s, 3), 2.10 (m, 2) ppm.

To 2-[(3-aminopropyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide (0.3 g, 0.7 mmol) (a compound of formula (Yc6)) dissolved in pyridine (5 mL) was added acetic anhydride (0.10 mL, 1.0 mmol). After stirring for 16 hours, the reaction was partitioned with ethyl acetate and water. The organic layer was separated, washed with water and brine, dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography on silica with CH_2Cl_2 gave 0.14 g of 2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide, a compound of formula (Yc7); NMR (DMSO-d_6) 8.4 (s, 1), 8.05 (t, 2), 7.85 (t, 1), 7.8 (s, 1), 7.05 (s, 1), 6.7 (m, 2), 6.6 (m, 1), 6.2 (s, 1), 5.9 (s, 2), 4.1 (m, 2), 3-3.6 (m, 6), 2.6 (m, 2), 2.3 (m, 3), 1.8 (s, 3), 1.65 (m, 2) ppm.

The following compounds of formula (Yc7) and derivatives thereof were prepared in a similar manner with appropriately substituted starting materials:

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.65 (s, 1), 7.0 (s, 1), 6.55 (m, 2), 6.5 (s, 1), 6.45 (d, 1), 6.15 (br, 1), 5.95 (br, 1), 5.85 (s, 2), 4.1 (s, 2), 3.65 (br, 2), 3.45 (m, 2), 3.2 (dd,2), 2.9 (s, 3), 2.65 (t, 2), 2.35 (s, 3), 1.9 (m, 2) ppm;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.7 (s, 1), 7.1(s, 1), 6.55 (d, 1), 6.5 (s, 1), 6.45 (d, 1), 6.3 (br, 1), 6.1 (br, 1), 5.9 (s, 2), 4.1 (s, 2), 3.7 (s, 3), 3.5 (m, 2), 3.2 (dd, 2), 2.7 (t, 2), 2.4 (s, 3), 1.85 (m, 4) ppm;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.75 (s, 1), 7.1 (s, 1), 6.95 (d, 2), 6.7 (d, 2), 6.25 (br, 1), 6.15 (br, 1), 4.1 (s, 2), 3.75 (s, 3), 3.6 (br, 2), 3.5 (m, 2), 3.2 (dd, 2), 2.95 (s, 3), 2.7 (t, 2), 2.4 (s, 3), 1.85 (m, 2) ppm;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.75 (s, 1), 7.1 (s, 1), 6.9 (d, 2), 6.7 (d, 2), 6.2 (br, 1), 6.1 (br, 1), 4.05 (s, 2), 3.75 (s, 3), 3.65 (s, 2), 3.5 (s, 3), 3.2 (m, 2), 2.7 (t, 2), 2.4 (s, 3), 1.8 (m, 4) ppm;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide; NMR ($CDCl_3$) 8.45 (s, 1), 7.7 (s, 1), 7.05 (s, 1), 6.9 (d, 2), 6.65 (d, 2), 6.4 (br, 1), 6.1 (s, 1), 4.05 (s, 2), 3.7 (s, 3), 3.5 (m, 4), 3.25 (dd, 2), 2.7 (t, 2), 2.4 (s, 3), 1.9 (s, 3), 1.8 (m, 2) ppm;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.60 (s, 1), 7.78 (s, 1), 7.08 (s, 1), 6.64 (d, 1), 6.45 (s, 1), 6.44 (d, 1), 6.25 (br, 1), 6.15 (s, 1), 5.05 (br, 1), 4.12 (m, 6), 3.65 (s, 3), 3.45 (m, 4), 3.20 (m, 2), 2.65 (t, 2), 2.40 (s, 3), 1.80 (m, 2) ppm;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.50 (s, 1), 7.75 (s, 1), 7.06 (s, 1), 6.62

(d, 1), 6.58 (br, 1), 6.45 (s, 1), 6.42 (d, 1), 6.15 (s, 1), 4.10 (m, 6), 3.55 (m, 4), 3.30 (m, 2), 2.64 (t, 2), 2.40 (s, 3), 1.92 (s, 3), 1.82 (m, 2) ppm;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.46 (s, 1), 7.76 (s, 1), 7.03 (s, 1), 6.65 (d, 1), 6.50 (s, 1), 6.42 (d, 1), 6.18 (br, 1), 5.80 (br, 1), 4.20 (m, 6), 3.65 (br, 2), 3.48 (m, 2), 3.20 (m, 2), 2.92 (s, 3), 2.65 (m, 2), 2.40 (s, 3), 1.90 (m, 2) ppm;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.46 (s, 1), 7.76 (s, 1), 7.05 (s, 1), 6.86 (s, 1), 6.72 (d, 1), 6.55 (d, 1), 6.45 (br, 2), 6.13 (s, 1), 4.50 (t, 2), 4.08 (s, 2), 3.55 (m, 4), 3.30 (q, 2), 3.06 (t, 2), 2.66 (t, 2), 2.40 (s, 3), 1.93 (s, 3), 1.85 (m, 2) ppm;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.46 (s, 1), 7.76 (s, 1), 7.05 (s, 1), 6.84 (s, 1), 6.70 (d, 1), 6.54 (d, 1), 6.26 (br, 2), 6.10 (s, 1), 5.08 (br, 1), 4.50 (t, 2), 4.06 (s, 2), 3.65 (s, 3), 3.50 (m, 4), 3.22 (q, 2), 3.04 (t, 2), 2.66 (t, 2), 2.42 (s, 3), 1.80 (m, 2) ppm; and

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide; NMR ($CDCl_3$) 8.44 (s, 1), 7.74 (s, 1), 7.02 (s, 1), 6.86 (s, 1), 6.72 (d, 1), 6.52 (m, 2), 6.19 (s, 2), 5.80 (br, 1), 4.50 (t, 2), 4.10 (s, 2), 3.62 (br, 2), 3.46 (q, 2), 3.20 (q, 2), 3.06 (t, 2), 2.95 (s, 3), 2.66 (t, 2), 2.38 (s, 3), 1.86 (m, 2) ppm.

To 2-[(3-aminopropyl)[2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide (135 mg, 0.32 mmol) (a compound of formula (Yc6)) in pyridine (1.5mL) was added water (1.5 mL) solution of potassium cyanate (64 mg, 0.76 mmol). The mixture was stirred and heated in an oil bath at 80°C overnight. The mixture was poured into water and extracted with ethyl acetate (3x20mL). The combined ethyl acetate fractions were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (9:1 CH_3CN/NH_4OH) to afford 2-[[3-(ureido)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide, a compound of formula (Yc9); as a white solid; NMR (DMSO-d_6, 90 C) 8.4 (s, 1), 7.8 (s, 1), 7.05 (d, 2), 7.0 (s, 1), 6.75 (d, 2), 6.4 (s, 1), 4.1 (s, 2), 3.7 (s, 3), 3.5 (m, 2), 3.25 (m, 2), 3.05 (m, 2), 2.65 (t, 2), 2.3 (s, 3), 1.7 (m, 2) ppm.

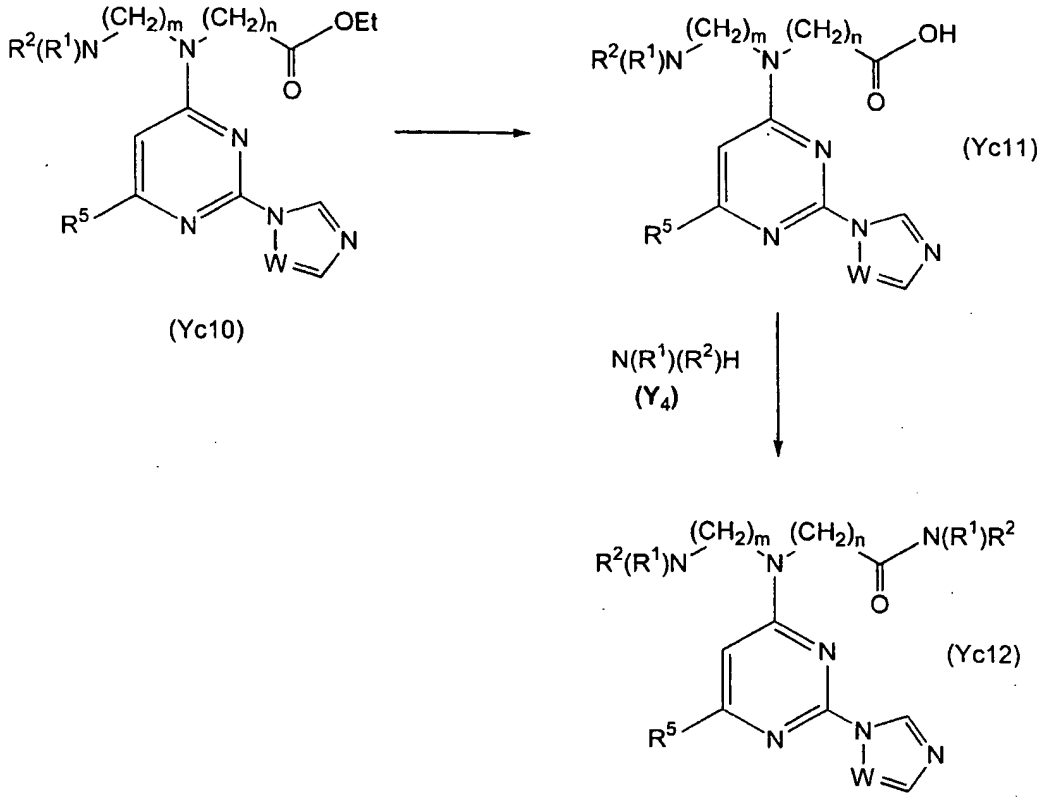
The following compounds of formula (Yc9) and derivatives thereof were prepared in a similar manner with the appropriately substituted starting materials:

2-[[3-(ureido)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; NMR (DMSO-d_6) 8.42 (br, 1), 8.08 (t, 1), 7.80 (br, 1), 7.05 (s, 1), 6.60 (m, 3), 6.03 (br, 1), 5.45 (br, 1), 4.18 (br, 6), 3.40 (m, 6), 3.00 (m, 2), 2.55 (m, 2), 2.35 (br, 3), 1.70 (m, 2) ppm; and

2-[[3-(ureido)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide; NMR (DMSO-d_6) 8.45 (br, 1), 8.12 (br, 1), 7.80 (br, 1), 7.00 (m, 2), 6.82 (m, 1), 6.60 (br, 1), 6.10 (br, 1), 5.42 (br, 1), 4.42 (t, 2), 4.14 (m, 2), 3.00-3.60 (m, 10), 2.60 (m, 2), 2.30 (s, 3), 1.68 (m, 2) ppm.

Reaction Scheme 4 depicts another method of preparing compounds of formula (Yc). Compounds of formula (Ya) and formula (Yb) may be similarly prepared.

Reaction Scheme 4



Compounds of formulae (Yc10) are prepared by methods disclosed herein. Each R^1, R^2, m and n are independently as described above in the Summary of the Invention for compounds of formula (Ya), formula (Yb) and formula (Yc); and R^5 and W are also as described above in the Summary of the Invention for compounds of formula (Ya), formula (Yb) and formula (Yc).

The above synthesis may be carried out as follows:

To 2-[[3-[(1,3-benzodioxol-5-ylmethyl)amino](methyl)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid, ethyl ester (2.2 g, 4.6 mmol) (a compound of formula (Yc10)) dissolved in THF (50 mL) was added LiOH (0.34 g, 8.1 mmol) and water (10 mL). After stirring for 16 hours, the solvent was removed in vacuo and 1 N HCl (8.1 mL, 8.1 mmol) was added. The solvent was removed in vacuo to give 2-[[3-[(1,3-benzodioxol-5-

ylmethyl)(methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid, a compound of formula (Yc11).

To 2-[[3-[(1,3-benzodioxol-5-ylmethyl)(methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid (0.35 g, 0.8 mmol) (a compound of formula (Yc11)) slurried in DMF (5 mL) was added carbonyldiimidazole (0.14 g, 0.8 mmol). After stirring for 20 minutes, diethylamine (0.25 mL, 2.4 mmol) was added. After stirring for 18 hours, the reaction was partitioned with ethyl acetate and water. The organic layer was separated, washed with water, dried (Na_2SO_4), and the solvent was removed in vacuo to give 0.91 g of the desired product. Chromatography on silica with CH_2Cl_2/ MeOH gave 2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*,*N*-diethylacetamide; NMR ($CDCl_3$) 8.4 (s, 1), 7.85 (s, 1), 7.1 (m, 1), 6.85 (s, 1), 6.75 (m, 2), 6.4 (br, 1), 5.95 (s, 2), 4.4 (br, 2), 3.6 (br, 2), 3.4 (m, 6), 2.45 (t, 2), 2.35 (s, 3), 2.2 (s, 3), 1.9 (m, 2), 1.3 (t, 3), 1.15 (t, 3) ppm.

The following compounds of formula (Yc12) and derivatives thereof were prepared in a similar manner:

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-(2-dimethylaminoethyl)acetamide; NMR ($CDCl_3$) 8.5 (s, 1), 7.8 (s, 1), 7.1 (s, 1), 6.8 (s, 1), 6.75 (m, 2), 6.25 (br, 1), 5.95 (s, 2), 4.15 (br, 2), 3.6 (br, 2), 3.4 (s, 2), 3.35 (m, 2), 2.4 (t, 2), 2.4 (s, 3), 2.35 (t, 2), 2.2 (s, 3), 2.0 (br, 6), 1.8 (m, 2), 1.6 (m, 2) ppm; and

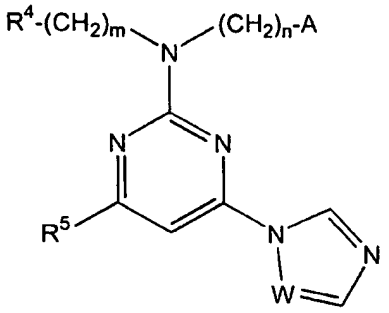
2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide; NMR (DMSO-d_6) 8.4 (s, 1), 7.8 (s, 1), 7.5 (s, 1), 7.1 (m, 2), 6.8 (m, 3), 6.3 (br, 1), 6.0 (s, 2), 5.4 (br, 1), 4.1 (m, 2), 3.4 (m, 4), 2.4 (t, 2), 2.3 (s, 3), 2.1 (s, 3), 1.75 (m, 2) ppm.

* * * * *

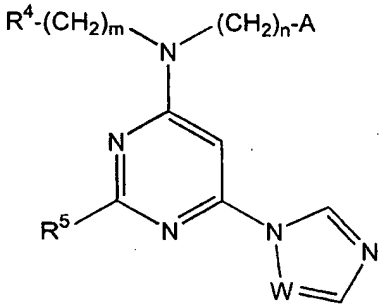
While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

What is claimed is:

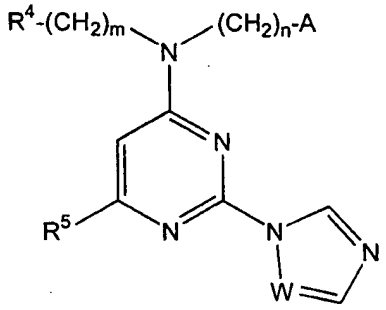
1. A compound of formula (Ya), formula (Yb) or formula (Yc):



(Ya);



(Yb);



(Yc);

wherein:

n and m are independently an integer from 1 to 4;

A is $-C(O)OR^1$ or $-C(O)N(R^1)R^2$;

each W is N or CH;

each R^1 is independently hydrogen, alkyl, aryl or aralkyl;

each R^2 is independently hydrogen, C_1-C_{20} alkyl, $-(CH_2)_n-N(R^1)_2$, heterocyclylalkyl (optionally substituted by alkyl, halo, haloalkyl or alkoxy), aralkyl (optionally substituted by halo, alkyl, alkoxy, or $-N(R^1)_2$);

when m is an integer from 2 to 4, R^4 can be hydroxy, $-N(R^1)R^2$, $-N(R^1)-C(O)-R^1$, $-N(R^1)-C(O)OR^1$, $-N(R^1)-S(O)_t-R^1$, or $-N(R^1)-C(O)-N(R^1)_2$;

when m is an integer from 1 to 4, R^4 can also be cyano or heterocyclyl;

R^5 is hydrogen, halo, alkyl, aryl, aralkyl, or haloalkyl;

as a single stereoisomer or mixture thereto, or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 having the formula (Yc) wherein:

n is 1;

m is 2 or 3;

A is $-C(O)OR^1$ or $-C(O)N(R^1)R^2$;

each W is CH;

R^1 is hydrogen or alkyl; and

R^2 is hydrogen, alkyl, $-(CH)_n-N(R^1)_2$, optionally substituted heterocyclylalkyl or optionally substituted aralkyl.

3. The compound of Claim 3 wherein R^4 is $-N(R^1)R^2$ where R^1 is hydrogen or alkyl and R^2 is heterocyclylalkyl selected from the group consisting of (1,3-benzodioxol-5-yl)methyl or (1,4-benzodioxan-6-yl)methyl.

4. The compound of Claim 4 selected from the group consisting of:

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetic acid, ethyl ester;

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N,N*-diethylacetamide;

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-(2-dimethylaminoethyl)acetamide;

2-[[3-[[(1,3-benzodioxol-5-yl)methyl](methyl)amino]propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide;

2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N,N*-diethylacetamide;

2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-methylacetamide;

2-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-methylacetamide;

2-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N,N*-diethylacetamide;

2-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide; and

2-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]acetamide.

5. The compound of Claim 2 wherein R^4 is heterocyclyl.

6. The compound of Claim 5 selected from the group consisting of:

2-[[pyridin-3-ylmethyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(*1H*-imidazol-1-yl)-6-methylpyrimidin-4-yl][(1,3-benzodioxol-5-yl)methyl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide; and

2-[[2-(*1H*-imidazol-1-yl)-6-methylpyrimidin-4-yl][2-(morpholin-4-yl)ethyl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide.

7. The compound of Claim 2 wherein R^4 is hydroxy, cyano, $-N(R^1)R^2$, $-N(R^1)-C(O)-R^1$, $-N(R^1)-C(O)OR^1$, $-N(R^1)-S(O)_t-R^1$, or $-N(R^1)-C(O)-N(R^1)_2$, where each R^1 and each R^2 is independently hydrogen, alkyl or aralkyl.

8. The compound of Claim 7 selected from the group consisting of:

2-[[3-hydroxypropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-cyanoethyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(di(phenylmethyl)amino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(ureido)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[3-(phenylmethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

2-[[3-aminopropyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

2-[[3-(dimethylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

2-[[3-(acetylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

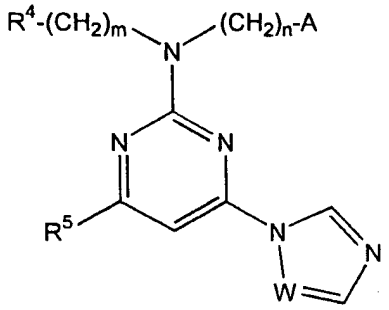
2-[[3-(methoxycarbonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

2-[[3-(methylsulfonylamino)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide;

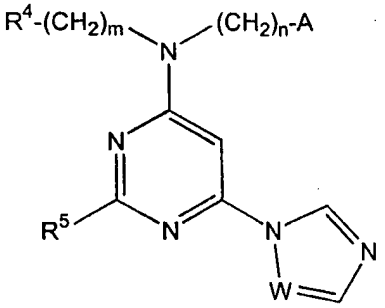
2-[[3-(ureido)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide; and

2-[[3-(ureido)propyl][2-(1*H*-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-*N*-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]acetamide.

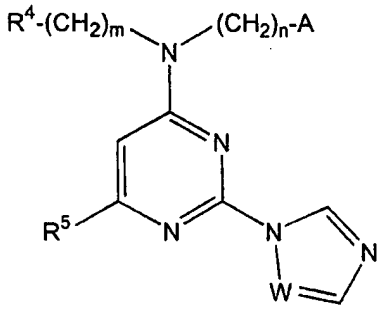
9. A pharmaceutical composition comprising a compound of formula (Ya), formula (Yb) or formula (Yc):



(Ya);



(Yb);



(Yc);

wherein:

n and m are independently an integer from 1 to 4;

A is $-C(O)OR^1$ or $-C(O)N(R^1)R^2$;

each W is N or CH;

each R^1 is independently hydrogen, alkyl, aryl or aralkyl;

each R^2 is independently hydrogen, C_1-C_{20} alkyl, $-(CH_2)_n-N(R^1)_2$, heterocyclylalkyl (optionally

substituted by alkyl, halo, haloalkyl or alkoxy), aralkyl (optionally substituted by halo, alkyl, alkoxy, or -$N(R^1)_2$);

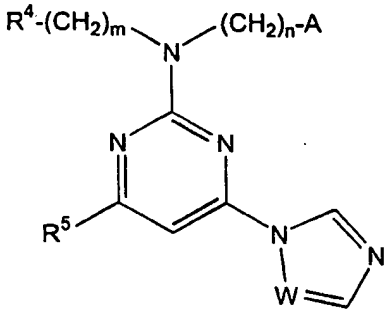
when m is an integer from 2 to 4, R^4 can be hydroxy, -$N(R^1)R^2$, -$N(R^1)$-C(O)-R^1, -$N(R^1)$-C(O)OR^1, -$N(R^1)$-$S(O)_t$-R^1, or-$N(R^1)$-C(O)-$N(R^1)_2$;

when m is an integer from 1 to 4, R^4 can also be cyano or heterocyclyl;

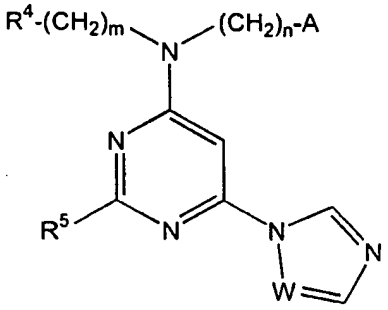
R^5 is hydrogen, halo, alkyl, aryl, aralkyl, or haloalkyl;

as a single stereoisomer or mixture thereto, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient thereof.

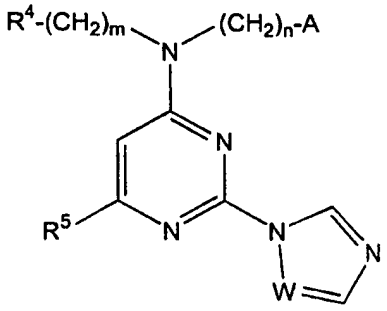
10. A method of treating a condition resulting from an abnormality in nitric oxide production which comprises administering to a mammal having a condition resulting from an abnormality in nitric oxide production a therapeutically effective amount of a compound of formula (Ya), formula (Yb) or formula (Yc):



(Ya) ;



(Yb) ;



(Yc) ;

wherein:

n and m are independently an integer from 1 to 4;

A is $-C(O)OR^1$ or $-C(O)N(R^1)R^2$;

each W is N or CH;

each R^1 is independently hydrogen, alkyl, aryl or aralkyl;

each R^2 is independently hydrogen, C_1-C_{20} alkyl, $-(CH_2)_n-N(R^1)_2$, heterocyclylalkyl (optionally substituted by alkyl, halo, haloalkyl or alkoxy), aralkyl (optionally substituted by halo, alkyl, alkoxy, or $-N(R^1)_2$);

when m is an integer from 2 to 4, R^4 can be hydroxy, $-N(R^1)R^2$, $-N(R^1)-C(O)-R^1$, $-N(R^1)-C(O)OR^1$, $-N(R^1)-S(O)_t-R^1$, or $-N(R^1)-C(O)-N(R^1)_2$;

when m is an integer from 1 to 4, R^4 can also be cyano or heterocyclyl;

R^5 is hydrogen, halo, alkyl, aryl, aralkyl, or haloalkyl;

as a single stereoisomer or mixture thereto, or a pharmaceutically acceptable salt thereof.

11. The method according to Claim 10 wherein said condition resulting from an abnormality in nitric oxide production is chosen from the group consisting of multiple sclerosis, stroke or cerebral ischemia, Alzheimer's disease, HIV dementia, Parkinson's disease, meningitis, dilated cardiomyopathy and congestive heart failure, atherosclerosis, restenosis or graft stenosis, septic shock and hypotension, hemorrhagic shock, asthma, adult respiratory distress syndrome, smoke or particulate-mediated lung injury, pathogen-mediated pneumonias, trauma of various etiologies, rheumatoid arthritis and osteoarthritis, glomerulonephritis, systemic lupus erythematosus, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, insulin dependent diabetes mellitus, diabetic neuropathy or nephropathy, acute and chronic organ transplant rejection, transplant vasculopathies, graft-versus-host disease, psoriasis and other inflammatory skin diseases, and cancer.

12. The method of Claim 11 wherein the condition is multiple sclerosis.

13. The method of Claim 11 wherein the condition is rheumatoid arthritis.

14. The method of Claim 11 wherein the condition is dilated cardiomyopathy.

15. The method of Claim 11 wherein the condition is congestive heart failure.

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/US 00/23173

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/14 C07D403/04 A61K31/506 A61P21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 37079 A (BERLEX LABORATORIES INC.) 27 August 1998 (1998-08-27) claims	1-15
A	EP 0 640 599 A (ONO PHARMACEUTICAL CO) 1 March 1995 (1995-03-01) claims	1-15
A	WO 93 17009 A (ZENYAKU KOGYO KK) 2 September 1993 (1993-09-02) claims	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 January 2001	15/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/US 00/23173

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9837079 A	27-08-1998	AU	6174998 A	09-09-1998
		CN	1252799 T	10-05-2000
		EP	0968206 A	05-01-2000
		GB	2338957 A	12-01-2000
		NO	993996 A	18-10-1999
		PL	335235 A	10-04-2000
EP 0640599 A	01-03-1995	AT	163647 T	15-03-1998
		CA	2130878 A,C	27-02-1995
		CN	1109055 A	27-09-1995
		DE	69408750 D	09-04-1998
		DE	69408750 T	23-07-1998
		DK	640599 T	28-09-1998
		ES	2114662 T	01-06-1998
		JP	7089958 A	04-04-1995
		KR	204433 B	15-06-1999
		US	5525604 A	11-06-1996
WO 9317009 A	02-09-1993	AU	3575193 A	13-09-1993
		CA	2131004 A	02-09-1993
		DE	69322076 D	17-12-1998
		EP	0629622 A	21-12-1994
		US	5489591 A	06-02-1996